REMARKS

I. Introduction

Upon entry of the present amendment, claims 1-6 and 8-16 will be pending in this application. The Examiner has objected to the drawings, the abstract, and the arrangement of the specification. Appropriate corrections are submitted. The Examiner has also objected to claim 6 as being in improper dependent form. Applicants have rewritten claim 6 in independent form. Applicants have also incorporated claim 7 into claim 1 to clarify claim 1 and cancelled claim 7 without prejudice or disclaimer.

The Examiner has rejected claims 13 and 17 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants have amended claim 13 for clarification and have cancelled claim 17. The Examiner has also rejected:

- claims 1, 3-8, 12-14, and 17 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Ecker (U.S. Patent No. 5,641,625);
- claims 9-11, 15, and 16 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Ecker (U.S. Patent No. 5,641,625) in further view of Wang (J. Am Chem. Soc. Vol. 119, pp. 7667-70 1996); and
- claims 1-8, 13, 14 and 17 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Frank-Kamenetskii (WO 97/14793).

Applicants respectfully traverse these rejections and request reconsideration and withdrawal thereof for the reasons set forth in Section IV below.

II. Drawings

The Examiner has objected to the key in Figure 2, asserting that the drawing does not explain the drawing. Applicants agree. We are in the process of clarifying the drawing with the inventors and will submit an appropriate correction as soon as possible.

III. Arrangement of Specification

The Examiner has objected to the abstract. A revised abstract is submitted with this response.

The Examiner has also objected to the arrangement of the specification. Appropriate correction has been made.

The Examiner has further objected to the misspelling of polypyrimidine on page 5 of the specification. Appropriate correction has been made.

IV. Claims

A. Claim 6

The Examiner has objected to claim 6 and being of improper dependent form. Applicants have rewritten claim 6 in independent form.

B. 35 U.S.C. § 112

The Examiner has rejected claims 13 and 17 under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants have amended claim 13 to clarify the features of the primer. Applicants have cancelled claim 17.

C. Vary in view of Ecker

The Examiner has rejected claims 1, 3-8, 12-14, and 17 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Ecker (U.S. Patent No. 5,641,625). The Examiner's position is that Vary teaches the use of a probe for detection of a nucleic acid

sequence target by formation of a triple helix which eliminates denaturation during detection. Vary is further characterized as teaching the detection of amplification of product duplexes. The Examiner states that the triple helix forming duplex sequences may be endogenous to target sequence or they may be introduced by probes during PCR amplification by primers, and that the target sequence contains a polypurine region and the probe contains a high polypyrimidine. The Examiner further asserts that Vary teaches introducing a polypyrimidine on the 5' end of a primer to introduce high polypurine target into amplified DNA. However, the section of Vary to which the Examiner cites in support of the high polypurine target (page 30, lines 15-20), does not actually teach a high polypurine target. The example at page 30 of Vary does not use a primer with a high polypyrimidine, and the resulting target also does not have a high polypurine content. In fact, there is no teaching in the Vary reference to introduce a purine rich region into the target sequence during the amplification reaction.

The Examiner acknowledges that Vary does not teach the use of a peptide nucleic acid, but asserts that one of ordinary skill in the art would have been motivated to apply the PNA probes described by Ecker to the teachings of Vary in order to provide a probe that binds specifically to a target sequence. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

The cited references are not properly combinable, and even if combined, they do not teach each claim limitation recited by Applicants. First, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the

art. *See In re Fine,* 837 F.2d 1071 (Fed. Cir. 1988); *In re Jones,* 958 F.2d 327 (Fed. Cir. 1992). However, one or ordinary skill in the art would not be motivated to combine the Vary and Ecker references.

The Vary reference is directed to amplifying a nucleic acid target sequence to provide product duplexes and detecting the product duplexes by hybridizing a third strand of nucleic acid to the product duplex to form a triple helix nucleic acid structure. The third strand may include a polypyrimidine sequence or a purine sequence. See abstract, pages 3-4.

By contrast, the Ecker reference describes the use of peptide nucleic acids (PNA) to form triplex structures in order to modulate protein activity. The reference as a whole is primarily directed to therapeutic uses of the PNA to cleave double-stranded DNA, activate or inhibit certain genes, initiate transcription, inhibit action of restriction enzymes and so forth. It is not directed toward detecting target sequences, but instead, modifying protein activity.

One of ordinary skill in the art would not be motivated to select the therapeutic peptide nucleic acid described by the Ecker reference for use in the detection process of Vary. There is no suggestion in the Vary reference to modify the nucleic acid probe to provide a peptide nucleic acid.

Furthermore, even if the references were properly combinable, their combination does not teach every element of Applicants' claimed invention. In order to establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art. See *In re Ryka,* 490 F.2d 981 (CCPA 1974) (emphasis added). Claim1 has been amended to specify that a purine rich region is introduced during amplification. Neither the Vary or the Ecker reference suggests amplifying a target nucleic acid and ***introducing a purine rich region***

into the target sequence during the amplification reaction so that the product of the amplification reaction includes a purine rich region.

In Vary, the third strand - the strand that the Applicants believe the Examiner is comparing to Applicants' claimed PNA - is the strand that "includes a polypyrimidine sequence" or a "polypurine sequence," see pages 3-4, not the target nucleic acid. There is no teaching in Vary to amplify the target nucleic acid itself to produce a target nucleic acid with a purine rich region as Applicants claim, but instead the purine rich region is provided on the third strand.

In Ecker, the only references to a "purine rich" region are (1) at column 11, lines 1-3, where a definition of "purine rich" is provided, but not discussed further and (2) at column 35, lines 60-65, where the PNA has an adenosine rich region to mitigate the effects of pH. Again, similar to the Vary reference, this is the PNA, ***not the target sequence,*** that has a purine rich region. Thus, even if the references were properly combinable (which Applicants dispute), there is no teaching or suggestion to ***amplify the target nucleic acid*** to provide a target sequence purine rich region. With respect to amended claim 6, the combination of the references also does not specifically suggest providing a target nucleic acid that contains a purine rich region and amplifying the target nucleic acid so that the product of the amplification reaction includes the purine rich region. As such, Applicants respectfully request that this rejection be withdrawn and that claims 1, 3-8, and 12-14 be held allowable.

D. Vary in view of Ecker in further view of Wang

The Examiner has rejected claims 9-11, 15, and 16 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Ecker (U.S. Patent No. 5,641,625) in further view of Wang (J. Am Chem. Soc. Vol. 119, pp. 7667-70 1996). The Examiner

admits that Vary does not teach a biosensor, but asserts that Wang teaches a biosensor attached to PNA probes for detection. The Examiner's position is that one of ordinary skill in the art would have been motivated to apply the Wang biosensor PNA surface probes to the combined invention of Vary and Ecker in order to increase the high throughput and sensitivity of detection. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

First, the arguments submitted above against the combination and applicability of the Vary and Ecker references are incorporated herein by this reference. Additionally, the Wang reference also fails to suggest ***amplifying the target nucleic acid to provide a purine rich region***. Thus, the combination of the references fails to teach every element of claim 1, upon which claims 9-11, 15, and 16 depend. At least for this reason, Applicants assert that the rejection should be withdrawn and that claims 9-11, 15 and 16 should be held allowable.

E. Vary in view of Frank-Kamenetskii

The Examiner has also rejected claims 1-8, 13, 14 and 17 under 35 U.S.C. § 103(a) as unpatentable over Vary (WO 92/11390) in view of Frank-Kamenetskii (WO 97/14793). The Examiner characterizes Vary as described above and admits that Vary does not teach a bis-peptide. The Examiner asserts that Frank-Kamenetskii teaches a bis-PNA for binding to double strand DNA, that the PNA clamps show high stability, and that they may be used in PCR to avoid competing side reactions such as amplification of non-target sequences in background and primer oligomerization. The Examiner's position is that one of ordinary skill in the art would have been motivated to apply Frank-Kamenetskii's probes to Vary's detection method to provide a probe that binds specifically to a target sequence. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

First, the Vary reference and the Frank-Kamenetskii reference are not properly combinable. Frank-Kamenetskii is directed to nucleic acid clamps that are intended to inhibit or prevent amplification, selectively cleave nucleic acids, or to regulate gene expression in the treatment of disorders. The clamp may be hybridized to a target nucleic acid at a binding site to form a triple helix and the triple helix inhibits interaction between the nucleic acid and the protein. There is no suggestion to use the clamp to detect the presence of a product. On the other hand, the Vary reference is primarily directed to sequence detection. The references relate to different areas of endeavor, and one of ordinary skill in the art would not be motivated to combine the references together

Furthermore, even if the references were properly combinable, their combination does not teach every element of Applicants' claimed invention. Neither Vary or Frank-Kamenetskii suggest amplifying a target nucleic acid and introducing a purine rich region into the target sequence during the amplification reaction so that the product of the amplification reaction includes a purine rich region.

Applicants incorporate the above arguments with respect to Vary. Briefly, there is no teaching to amplify the target nucleic acid itself to produce a purine rich region as Applicants claim. Instead, Vary describes a purine rich region on the third strand.

The Frank-Kamenetskii reference also fails to provide a target nucleic acid sequence with a "purine rich" region. Thus, even if the references were properly combined (which Applicants dispute), there is no teaching or suggestion in either reference, alone or in combination, to amplify the target nucleic acid to provide an amplification product with a purine rich region. As such, Applicants respectfully request that this rejection be withdrawn and that claims 1-8, 13, 14 and 17 be held allowable.

Version with markings to show changes made:

In the specification

On page 1, line 3, after the title, kindly insert this paragraph in place of the first paragraph:

--This application claims priority to Great Britain Application No. 9815933.8 filed on July 23, 1998 and International Application Publication Number WO/00/05408 filed on July 19, 1999.

Background of the Invention

1. Field of the Invention

The present invention relates to a method of detecting specific target DNA sequences, and in particular to the products of amplification reactions, as well as to reagents and apparatus used in that method.

2. Description of the Related Art--.

On page 2, line 10, kindly insert:

--Summary of the Invention--.

On page 5, line 30, kindly insert:

--Brief Description of the Drawings--.

On page 5, lines 30-33, kindly rewrite the paragraph as follows:

--Figure 2 illustrates diagrammatically the incorporation of purine rich regions into an amplification product, using 5' – tagging of primers with polypyrimidine sequences;--.

On page 6, line 3, kindly insert:

--Detailed Description of the Invention--.

In the claims:

Kindly cancel claims 7 and 17 without prejudice or disclaimer to the subject matter thereof.

Kindly amend the claims as follows:

1. (Amended) A method for detecting the presence of a target nucleic acid sequence in a sample, said method comprising:

(a) amplifying said target nucleic acid and introducing a purine rich region into the target sequence during the amplification reaction so that the product of the amplification reaction includes a purine rich region;

(b) contacting the sample with a peptide nucleic acid able to bind at least a portion of said target sequence; and

(c) detecting the presence of triplex structures,

wherein the detection of the presence of triplex structures indicates the presence of target nucleic acid sequences in the sample.

6. (Amended) A method [according to claim 1] for detecting the presence of a target nucleic acid sequence in a sample, said method comprising:

(a) providing a target nucleic acid that [wherein the target nucleic acid] contains a purine rich region;

(b) amplifying said target nucleic acid so that the product of the amplification reaction includes the purine rich region;

(c) contacting the sample with a peptide nucleic acid able to bind at least a portion of said target sequence; and

(d) detecting the presence of triplex structures,

wherein the detection of the presence of triplex structures indicates the presence of target nucleic acid sequences in the sample.

8. (Amended) A method according to claim [7] 1 wherein primers used in the amplification comprise a plurality of pyrimidines at the 5' end thereof.

13. (Amended) [The use of a] A primer, comprising a sequence which hybridizes to an end region of a target nucleic acid sequence, and a plurality of pyrimidine residues at a 5' region thereof, [in a method according to claim 1], wherein the primer is adapted to introduce a purine rich region into an amplification product so that the product of the amplification reaction includes a purine rich region.

CONCLUSION

For at least the above reasons, Applicant respectfully requests allowance of claims 1-6 and 8-16 and issuance of a patent containing these claims in due course. If there remain any additional issues to be addressed, the Examiner is invited to contact the undersigned attorney.

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. 1.136(a), Applicant petitions that the period for response to the Office Action dated July 3, 2002 in connection with the above-identified application be extended for one month, to and including November 3, 2002 which is a Sunday. A check for this extension is enclosed. The Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Deposit Order Account No. 11-0855.

Respectfully submitted,

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